1198-5 **Efficacy of Activation of Peroxisome Proliferative-Activated Receptors (PPAR)-a on Vasular Remodeling After Coronary Angioplasty: Possible Role of Endothelial Dysfunction and Collagen Accumulation**

Katsumi Miyauchi, Takeshi Kurata, Takayuki Yokoyama, Yoshinori Akimoto, Kouichiro Aihara, Kazunori Shimada, Hitoshi Satoh, Hiroyuki Daida, *Juntendo University, Tokyo, Japan.*

Constrictive remodeling plays a prominent role in restenosis after balloon angioplasty. The severity of constrictive remodeling correlates with endothelium dependent relaxation and collagen density. At the site of coronary angioplasty, inflammatory cytokine can induce chain reaction that may cause restenosis, and PPAR-a activation suppresses the inflammatory cytokines. Fenofibrate is a hypolipidemic drug, the PPAR-a specific ligand that has been shown to enhance PPAR-a activity. Thus, fenofibrate may be proposed as a promising strategy against restenosis. We tested fenofibrate for its efficacy on remodeling, expression of collagen synthesis, and endothelial function in 14 coronary arteries of 7 pigs (1000mg/day orally beginning 7d pre-angioplasty) and was compared to placebo (14 coronaries, 7 pigs) 28 days after angioplasty. Quantitative intravascular ultrasound revealed fenofibrate increased lumen area compared with placebo (4.84±0.26 vs. 4.25±0.33mm2). Remodeling index was defined as the ratio the external elastic membrane (EEM) area at the lesion to that at the proximal reference site. EEM area (7.91±0.64 vs. 6.12±0.56mm2) and remodeling index (1.10 vs. 0.88) were significantly greater in fenofibrate than that in placebo. Histopathologic assessment showed that PPAR-a in neointima was up-regulated in fenofibrate group whereas there was a few positive cells in placebo. Collagen content was measured by a digital subtraction method (sirius red-stained sections) and was significantly decreased in the treated vessels compared to controls (75±11 vs. 88±9%). Assessment of endothelial function in vivo was performed 4 weeks after angioplasty. Balloon injured coronary arteries in placebo group showed an impaired relaxation to acetylcholine while relaxation to acetylcholine was reversed in the injured vessels derived from fenofibrate treated pigs (4.2±8.3 vs. 31.5±13%). In conclusion, pharmacological activation of PPAR-a inhibited constrictive remodeling after balloon angioplasty through reduction collagen synthesis and recovery of endothelium-dependent relaxation.

1198-25 **Effects of Simvastatin on the Response to Arterial Injury in Wild-Type (WT) and Apolipoprotein E-Deficient (ApoE0) Mice**

Robin P. Choudhury, Angela L. Carrelli, Joshua Stern, Raymond Soccio, Igor Chereshnev, Valerie Elmalem, John T. Fallon, Edward A. Fisher, Ernane D. Reis, *Mount Sinai School of Medicine, New York, New York.*

BACKGROUND. Statins suppress cell proliferation and promote endothelial restoration independent of cholesterol-lowering. We hypothesized that these properties may inhibit intimal hyperplasia after arterial injury. Normolipidemic (WT) and hyperlipidemic (ApoE0) mice were studied. Since ApoE0 mice lack the major ligand for LDL receptors, we hypothesized that simvastatin would not alter lipoprotein levels.
METHODS. Wild type (n=40) and ApoE0 (n=40) mice were fed chow. At age 10 weeks, 20 from each group were converted to chow containing simavastatin (100mg/kg/day). At age 12 weeks all mice underwent bilateral transluminal femoral artery injury with a 0.010" angioplasty guidewire. Arteries were perfusion-fixed after 4 weeks and analyzed.
RESULTS. (1)WT mice: Plasma cholesterol (mean/SD mg/dL) was similar in treated (101/19.8) and untreated (77.4/16.2) mice. FPLC showed no differences in lipoprotein profiles. Statins inhibit HMGCoA reductase and induce its transcription. To demonstrate an effective simvastatin dose, mRNA for HMGCoA Reductase was quantified by reverse transcriptase-PCR and shown to be increased 5.4-fold (P<0.0001) by simvastatin. Intimal hyperplasia, (IH = ratio of intima to media area) was similar in simvastatin treated (0.8+/-0.4) and untreated (0.7+/-0.4) mice.
(2)ApoE0 mice: Plasma cholesterol in untreated mice (658/258) was higher than in WTs (P<0.0001). Unexpectedly, simvastatin treatment caused a further increase to 1094/225.7 (P<0.0001). Untreated ApoE0 mice had higher I/M ratios than WTs (1.31+/-0.66 vs 0.7+/-0.4, P<0.001). This effect was exaggerated in the paradoxically hyperlipidemic simvastatin-treated mice whose intimal area was increased by a further 50% (P<0.02).
CONCLUSION. In WT mice, simvastatin: (1) induced HMGCoA reductase, (2) had no effect on plasma cholesterol or lipoprotein profiles (3) did not reduce intimal hyperplasia. In ApoE0 mice, (1) hyperlipidemia promoted IH (2) simvastatin worsened hyperlipidemia and IH. (3) It is speculated that in ApoE0 mice, where lipoprotein clearance is abnormal, small increases in lipoprotein production, secondary to upregulation of synthetic enzymes cause an increase in plasma cholesterol.

1198-26 **Photodynamic Therapy of Pig Coronary Arteries Induces Apoptosis of Endothelial and Vascular Smooth Muscle Cells**

Richard J. Mansfield, Nadim Malik, Alexander Mosse, Andrzej Loesch, Stephen Bown, Jean McEwan, *Royal Free & UCL Medical School, London, United Kingdom, Cardiovascular Research, Northern General Hospital, Sheffield, United Kingdom.*

Photodynamic therapy (PDT) may be useful in preventing restenosis. It involves the local activation of a systemically administered photosensitiser by non-thermal laser light. It induces endothelial denudation and vascular smooth muscle cell (SMC) ablation without inflammation with tissue architecture returning to normal within 4 weeks. We have shown previously that endovascular PDT inhibits neointima after experimental balloon injury. The mechanism of cell loss following PDT is the subject of this study.
Methods: 6 Large White-Landrace pigs (20-30Kg) were sensitised with iv 5-aminolaevulinic acid (60mg/Kg). Coronary angiography was performed 4 – 6 hours later and arteries randomised to either 50J/cm2 red light from a laser via a centering balloon catheter, sham illumination or no further treatment. Arteries from each group were harvested at 1,3 or 20 hours and processed for TUNEL staining including co-localisation immunohistochemistry for endothelial cells (von Willebrand factor - vWF), SMC (α-actin) and inflammatory macrophages (MAC 387), DNA fragmentation and transmission electron microscopy (TEM) to look for apoptosis. Mean cell counts were derived from 4 high power fields (HPF-x40 magnification), per section.
Results: There was no apoptosis in untreated vessels. 1 hour after PDT there was clear TUNEL staining of condensed nuclei of vWF-positive endothelial cells. Medial TUNEL and α-actin positive cells were seen at 3 and 20 hours with apoptotic cells constituting 5.4% and 10.3% of the total cells respectively. There were significantly fewer medial cells, with loss of α-actin positive staining, at 20 hours (45±14 vs 110±12 and 102±15 for PDT treated, sham illuminated and control arteries respectively, p<0.001). DNA fragmentation was seen at 20 hours only. Adventitial TUNEL positive cells were seen at 20 hours (9.7%). Inflammatory macrophages were not seen. Morphological features of endothelial and SMC apoptosis were confirmed on TEM at each time point after PDT.
Conclusion: PDT induces programmed cell death in endothelial and vascular smooth muscle cells. Reducing arterial cellularity by apoptosis may be one mechanism by which PDT has beneficial effects in restenosis.

ORAL CONTRIBUTIONS

872 Restenosis: New Antiproliferative Therapy

Tuesday, March 19, 2002, 4:00 p.m.-5:00 p.m.
Georgia World Congress Center, Room 254W

4:00 p.m.

872-1 **A Phase II Double Blind Placebo-Controlled Multicenter Study of the Anti-PDGF-β-R Di-Fab'-PEG Conjugate CDP860 (25 mg/kg) Dosed Intravenously in Patients Undergoing Elective Coronary Stent Placement**

Patrick W. Serruys, III, Guy Heyndrickx, Hans Bonnier, Matty Vrolix, Frank Van den Branden, Victor Legrand, Claude Hanet, Hans Te Riele, Michael Vandormael, Ivan De Scheerder, *Celltech Research and Development, Slough, Berkshire, United Kingdom.*

Coronary restenosis following angioplasty or stenting is a common problem which frequently requires re-intervention. A major element of restenosis is neointimal hyperplasia which particularly follows stent placement. In baboon models of restenosis, administration of an anti-PDGF-ß -receptor-blocking antibody potently inhibited vascular smooth muscle migration and subsequent neointimal hyperplasia.CDP860 consists of a humanised antibody di-Fab' against the ß -subunit of platelet derived growth factor receptor attached to polyethylene glycol. It is being evaluated in a phase II, double-blind placebo controlled trial in 10 centres in Belgium and the Netherlands for the prevention of within-stent restenosis. The primary efficacy endpoint is intravascular ultrasound comparison of mean percentage in-stent volume obstruction (PIVO) due to neointimal hyperplasia 6 months after dosing in CDP860 and placebo treated groups. Secondary endpoints are other IVUS and QCA parameters, incidence of restenosis, MACE and anginal status. Based on expected PIVO of 28.3%, it is calculated that 100 evaluable patients will be necessary to detect a 33% reduction by CDP860, with 85% power, at two sided α of 0.05. Patients with stable or unstable angina pectoris (Braunwald Class 1-3:B-C) or documented silent ischaemia who are eligible for elective stent placement in one or more coronary lesions, not treated within the last year in one or more native vessels, receive a single intravenous infusion of 25mg/kg CDP860 or placebo just prior to the procedure. Recruitment has been completed with 145 patients dosed. Treatment with study medication appears not to be associated with any serious safety concern. The study remains blinded. Six-month follow-up results will be presented at the meeting.

4:15 p.m.

872-2 **Combination of VEGF-C Gene Transfer and Treatment With the PDGF Receptor Kinase Inhibitor STI571 Leads to Persistent Reduction in Neointima Formation in Balloon-Denunded Rabbit Aorta**

Olli P. Leppanen, Mikko O. Hiltunen, Tuomas T. Rissanen, Juha Rutanen, Mikko P. Turunen, Tobias Sjöblom, Josef Brueggen, Marianne Carlsson, Elisabeth Buchdunger, David Bergqvist, Kari Alitalo, Carl-Henrik Heldin, Arne Östman, Seppo Ylä-Herttuala, *Ludwig Institute for Cancer Research, Uppsala, Sweden, A.I. Virtanen Institute for Molecular Sciences, Kuopio, Finland.*

Background: Several new therapies against neointima formation, such as inhibition of PDGF signaling to prevent smooth muscle cell growth, or application of endothelial cell mitogens of the VEGF family, have been recently developed and tested in various animal models. However, with these therapies lesion recurrence or 'catch-up growth' has been observed.
Methods: To evaluate the effects of combining inhibition of PDGF signaling with local application of VEGF-C on intimal thickening a rabbit model of restenosis was used. 42 rabbits were put on hypercholesterolemic diet and subjected to balloon injury. For VEGF-C application, local transfection with VEGF-C encoding replication-deficient adenoviruses was used. Inhibition of PDGF signalling was obtained by a 3-week course of systemic treatment with STI571, a potent low molecular weight inhibitor of PDGF-receptor tyrosine kinase.
Results: At an endpoint of 6 weeks after injury none of the therapies alone reduced intimal thickening. However, the combined treatment led to a persistent reduction (54% vs.